

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
13 January 2005 (13.01.2005)

PCT

(10) International Publication Number
WO 2005/003116 A1

(51) International Patent Classification⁷: **C07D 333/56**

(21) International Application Number:
PCT/EP2004/051263

(22) International Filing Date: 28 June 2004 (28.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2003A001333 30 June 2003 (30.06.2003) IT

(71) Applicant (for all designated States except US): **ER-REGIERRE S.p.A.** [IT/IT]; Via Francesco Baracca 19, I-24060 SAN PAOLO D'ARGON (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FERRARI, Massimo** [IT/IT]; Via Antonio Locatelli 7, I-24069 CENATE SOTTO (IT). **ZINETTI, Fabrizio** [IT/IT]; Via Valle 7, I-24060 CASAZZA (IT). **BELOTTI, Paolo** [IT/IT]; Via Cesare Battisti 5, I-24060 SAN PAOLO D'ARGON (IT).

(74) Agent: **GERVASI, Gemma**; **NOTARBARTOLO & GERVASI S.p.A.**, Corso di Porta Vittoria 9, I-20122 MILAN (IT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING RALOXIFENE HYDROCHLORIDE

(57) Abstract: Process for preparing raloxifene hydrochloride with a purity greater than 98% and low aluminium content comprising the following stages a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene in pyridine and hydrochloric acid to obtain 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene in pyridine hydrochloride, b) acetylation of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene, c) acylation of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene with 4-(2 piperidinoethoxy)benzoylchloride hydrochloride with aluminium trichloride in halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2 piperidinoethoxy)benzoyl]-benzo[b]thiophene, d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2 piperidinoethoxy)benzoyl]benzo[b]thiophene according to the following operating conditions: d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2 piperidinoethoxy)benzoyl]benzo[b]thiophene with alkaline hydroxide in alcohol solvent, d2) acidification of the product obtained in the preceding stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with the strong acid, characterised in that the strong acid used in stage (d2) is concentrated hydrochloric acid.

WO 2005/003116 A1